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Review

DNA methylation: New therapeutic implications for hepatic fibrosis

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ABSTRACT

DNA methylation refers to a heritable alteration in the pattern of gene expression that is regulated by a mechanism specifically not owing to changes in the primary nucleotide sequence. The transcriptional silencing caused by DNA methylation affects genes involved in the main cellular pathways: cell cycle control, Ras signaling, apoptosis, and detoxification. Recent studies have shown that methylation modifications orchestrate the activation of hepatic stellate cells (HSCs) characterized by excessive accumulation of extracellular matrices (ECMs). The activation of HSCs is mediated by multiple signal transduction pathways and is generally regarded as the major ECM producer responsible for liver fibrosis. In addition, aberrant methylation of specific gene involved in the activation of multiple signal transduction pathways in liver fibrosis. The aim of this review is to compile recent information on aberrant DNA methylation in hepatic fibrosis and to highlight key genes and molecular pathways in hepatic fibrosis formation.

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Contents

1. Introduction

Fibrosis of the liver and its end stage, cirrhosis, represent the final common pathway of virtually all chronic liver diseases. Liver fibrosis occurs as a pathological response to hepatitis viral infection and hepatotoxins such as ethanol, and is characterized by enhanced deposition of extracellular matrix (ECM) components [1,2]. At the present time, there are no specific treatments and limited treatments are available which are either removal of the underlying cause of liver injury or liver transplantation. It is therefore paramount that molecular mechanisms underlying fibrosis are elucidated as this may provide an ideal anti-fibrogenic therapy [3,4].

Myofibroblasts generated at sites of liver injury by transdifferentiation of resident cells are pivotal cellular elements of wound healing. A paradigm for this process is transition of hepatic stellate cells (HSCs) to hepatic myofibroblasts. In response to liver injury HSC undergoes a dramatic phenotypic change and becomes a myofibroblast-like cell with loss of vitamin A storage and marked upregulation of α-smooth muscle actin (α-SMA), collagen, tissue inhibitors of metalloproteinases (TIMP1) and desmin, and production of profibrogenic cytokines/growth factors such as transforming growth factor-β (TGF-β), and platelet-derived growth factor (PDGF) [5,6].

Such a dramatic phenotypic shift is underpinned by the loss of specific gene. Chromosomal deletions, mutations and amplifications play pivotal roles in these phenotypic transformations [7]. Evidence is now emerging to suggest that the repression of key genes is likely to be regulated by DNA methylation in hepatic fibrosis. The loss of

Abbreviations: HSCs, hepatic stellate cells; ECMs, extracellular matrices; α-SMA, α-smooth muscle actin; TGF-β, transforming growth factor-β; PDGF, platelet-derived growth factor; DNMTs, DNA methyltransferases; DNMT1, DNA methyltransferase 1; 5-Aza-dC, 5-Aza-2′-deoxycytidine; PTEN, phosphatase and tension homolog deleted on chromosome 10; RASAL1, Ras GTPase activating-like protein 1; MeCP2, methyl-CpG-binding protein 2; HDAC, histone deacetylases.

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key genes by DNA methylation contributed to the activation of pathways which were regulated by specific gene. In this regard, we have reviewed the growing body of evidence which suggests the loss of specific gene by DNA methylation, followed by the activation of signal pathways, leading to liver fibrosis (Fig. 1).

2. DNA methylation is involved in epigenetic silencing of gene

The term epigenetics refers to heritable changes in gene expression that are not caused by alterations in the DNA nucleotide sequence, but rather result from modification in the DNA backbone and DNA packaging [8–10]. DNA methylation so far is a well known epigenetic event. DNA is methylated by addition of a methyl group to the 5′position of cytosine residues in the cytosine-phosphoguanine (CpG) dinucleotide. This process is common throughout the genome, but when added to CpG dinucleotides in promoter region, CpG islands generally result in the loss of associated gene expression [11]. In cancer cells, where DNA methylation was the first epigenetic alteration to be observed, hypermethylation of CpG islands near tumor suppressor genes has been shown to switch off these genes [12,13]. Many tumor suppressor genes are repressed in tumorigenesis and progression. Although most of the work in hepatic fibrosis has focused on gene-silencing events caused by hypermethylation, it is important to mention that cytosine methylation can influence fibrosis by other mechanisms. It has been shown for example, that histone deacetylation or microRNA—another epigenetic event leading to transcriptional silencing can be stimulated by cellular machinery triggered by aberrant methylation [14–18] (Fig. 2).

3. DNA methyltransferases and their inhibitors

DNA methylation in mammalian cells is regulated by two general classes of DNA methyltransferases (DNMTs): maintenance DNMT1 and de novo DNMT3A and DNMT3B [19]. DNMT1 is mainly responsible for the maintenance of methylation pattern on the daughter strand after DNA methylation, while DNMT3A and DNMT3B are involved in the process of de novo methylation [20,21]. Hypermethylation at promoter CpG islands mediated by DNMTs is mainly responsible for epigenetic silencing of tumor suppressor genes. Inhibition of hypermethylation with methyltransferase inhibitors such as 5-Aza-2′-deoxycytidine (5-Aza-dC) can restore the expression of methylation silenced genes [22]. As DNMT inhibitors, 5-Aza-dC has been approved by the US Food and Drug Administration for the treatment of myelodysplastic syndrome and leukemia [23]. DNMT1 is rapidly degraded by the proteasomal pathway upon treatment of cells with 5-Aza-dC [24]. Inhibition of DNMT1 activity could reduce hypermethylation of repressive genes and promote its re-expression, and reverse phenotype of malignant tumor [25].

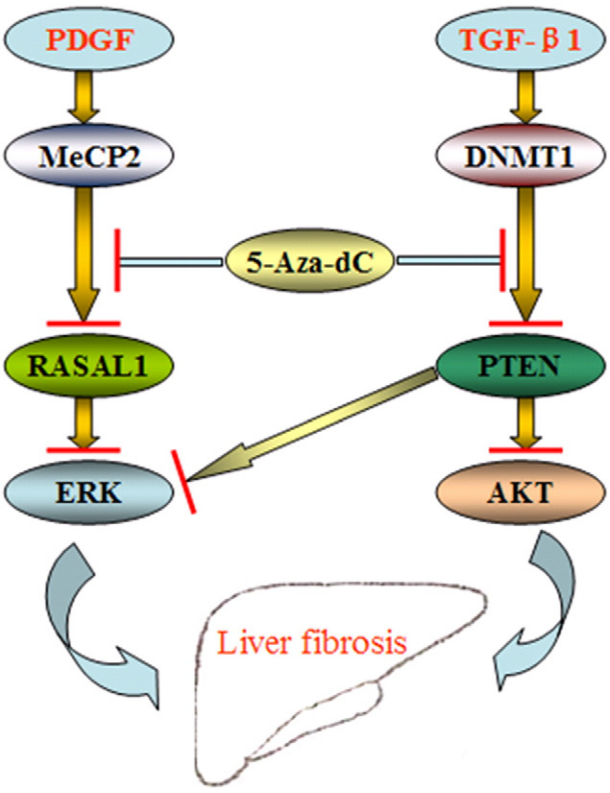

Fig. 1. Overview of the role of DNA methylation in liver fibrosis.

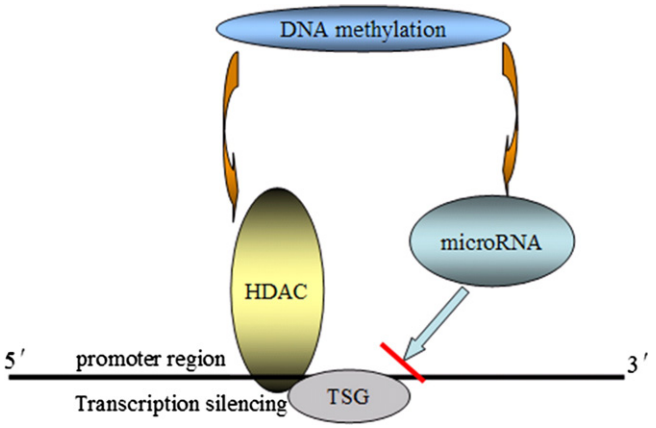

Fig. 2. Epigenetic repression of gene expression by DNA methylation. DNA methylation associated with histone deacetylases (HDAC) will be recruited to the tumor suppressor gene (TSG) a promoter leading to histone modification events associated with transcriptional repression. Silencing of TSG by microRNA is regulated by DNA methylation.

4. Epigenetic control of gene expression in HSC

Cells in the body are genetically identical but structurally and functionally heterogeneous due to differential expression of genes. These alterations occur during development, cell differentiation or in disease [26]. Although many genes are down-regulated such as anti-fibrosis genes, there are a large number of up-regulated genes including proinflammatory, profibrogenic genes that synergistically promote fibrosis [27–29]. Regulation of gene expression is an epigenetically governed process controlled by DNA methylation [30,31]. DNA methylation can alter the expression status of large numbers of genes in a cell at any one time. Therefore, improved understanding of the relationship between DNA methylation and gene transcription silencing provides new epigenetic paradigms with which to explain how liver fibrosis can be regulated.

A recent study from our laboratory researched the effect of the DNA methylation inhibitor 5-Aza-dC on the activation of HSC [32]. We demonstrated that treatment of TGF-β-induced HSC with 5-Aza-dC inhibited activation of HSC as demonstrated by the continued expression of phosphatase and tension homolog deleted on chromosome 10 (PTEN), a crucial antifibrotic proteins. In activated HSC, PTEN expression is reduced and its promoter is found in transcriptionally repressed chromatin structure.

In addition, 5-Aza-dC prevents PDGF-mediated loss of Ras GTPase activating-like protein 1 (RASAL1) expression which encodes an inhibitor of the RAS oncoprotein, which is involved in cellular signal transduction regulating cell growth, differentiation, and survival [33]. Taken together, these results suggest that DNA methylation was involved in cytokines induced HSC activated by silencing of specific gene.

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